IN THE SPECIFICATION:

On page 1, paragraph [0001]: This application is a continuation of copending International Patent Application PCT/US02/10849, which was filed on April 8, 2002, which designates the United States of America, which was published under the Patent Cooperation Treaty on October 17, 2002 as Publication Number WO 02/081640, and which (as filed and as published) is incorporated by reference in its entirety herein. This application also claims benefit of priority to Provisional Application Serial no. 60/281,779, filed April 6, 2001, which is incorporated by reference in its entirety herein.

On page 1, paragraph [0004]: Oligonucleotides have been employed as therapeutic moieties in the treatment of disease states in animals and man. For example, workers in the field have now identified antisense, triplex and other oligonucleotide compositions which are capable of modulating expression of genes implicated in viral, fungal and metabolic diseases. ~~tisense~~ Antisense oligonucleotide inhibition of gene expression has proven to be a useful tool in understanding the roles of raf genes. An antisense oligonucleotide complementary to the first six codons of human c-raf has been used to demonstrate that the mitogenic response of T cells to interteukin-2 (IL-2) requires c-raf. Cells treated with the oligonucleotide showed a near-total loss of c-raf protein and a substantial reduction in proliferative response to IL-2. Riedel et al., Eur. J. Immunol. 1993, 23, 3146-3150. Rapp et al. have disclosed expression vectors containing a raf gene in an antisense orientation downstream of a promoter, and methods of inhibiting raf expression by expressing an antisense Raf gene or a mutated Raf gene in a cell. WO application 93/04170. An antisense oligodeoxyribonucleotide complementary to codons 1-6 of murine c-Raf has been used to abolish insulin stimulation of DMA synthesis in the rat hepatoma cell line H4IIE. Tornkvistetal., J. Biol. Chem. 1994, 269, 13919-13921. WO Application 93/06248 discloses methods for identifying an individual at increased risk of developing cancer and for determining a prognosis and proper treatment of patients afflicted with cancer comprising amplifying a region of the c-raf gene and analyzing it for evidence of mutation. Denner et al. discloses antisense polynucleotides hybridizing to the gene for raf, and processes using them. WO 94/15645. Oligonucleotides hybridizing to human and rat raf sequences are disclosed. Iversen et al. discloses heterotypic antisense Oligonucleotides complementary to raf which are able to kill ras-activated cancer cells, and methods of killing raf-activated cancer cells. Numerous oligonucleotide sequences are disclosed, none of which are actually antisense oligonucleotide sequences.

On page 3, paragraph [0007]: It is an object of the invention to provide a gene that corresponds to a nucleic acid sequence comprising the nucleic acid sequence set forth in Figure 1 (~~SEQ ID NO 1~~ SEQ ID NO:1).

On page 3, paragraph [0008]: It is a more specific object of the invention to provide a SHINC-1 nucleic acid sequence identified in Figure 1 having ~~SEQ ID NO 1~~ SEQ ID NO:1.

On page 3, paragraph [0009]: It is another specific object of the invention to provide a nucleic acid sequence corresponding to nucleotides 1 to 485 of ~~SEQ ID NO 1~~ SEQ ID NO:1 contained in Figure 1 or a fragment thereof which is at least 100 nucleotides in length.

On page 3, paragraph [0010]: It is another object of the invention to provide a SHINC-1 polypeptide that ~~modulated~~ modulates apoptosis comprising an amino acid sequence which sequence is encoded by the nucleic acid sequence ~~depicted in Figure 1~~ of SEQ ID NO:1, or a fragment thereof which is at least 50 amino acids in length or an analog or homolog having at least 90% sequence identity to said polypeptide which modulates apoptosis.

On page 4-5, paragraph [0020]: **Figure 1. Partial cDNA sequence of Shinc-1 gene, SEQ ID NO:1**. The partial nucleotide sequence of a Shinc-1 cDNA fragment (456 bp) isolated from human prostate cancer cells (DU-145) by the differential display of mRNA approach shown (GenBank Accession no. AF316880). The nucleotide sequence representing the anchor primer and the arbitrary primer was confirmed as flanking sequence (data not shown). Based on the genomic database search, Shinc-1 gene is located on chromosome 8 (GenBank Accession no. AC084709, clone RP11-988M20).

On page 9-10, paragraph [0036]: Sequence identity or percent identity is intended to mean the percentage of same residues between two sequences, wherein the two sequences are aligned using the Clustal method (Higgins et al, Cabios 8:189-191, 1992) of multiple sequence alignment in the Lasergene biocomputing software (DNASTAR, INC, Madison, Wl). In this method, multiple alignments are carried out in a progressive manner, in which larger and larger alignment groups are assembled using similarity scores calculated from a series of pairwise alignments. Optimal sequence alignments are obtained by finding the maximum alignment score, which is the average of all scores between the separate residues in the alignment, determined from a residue weight table representing the probability of a given

amino acid change occurring in two related proteins over a given evolutionary interval. Penalties for opening and lengthening gaps in the alignment contribute to the score. The default parameters used with this program are as follows: gap penalty for multiple alignment=IO; gap length penalty for multiple alignment=10; k-tuple value in pairwise alignment=1; gap penalty in pairwise alignment=3; window value in pairwise alignment=5; diagonals saved in pairwise alignmentz=5. The residue weight table used for the alignment program is PAM25O (~~Dayhoffet~~ Dayhoff et al., in Atlas of Protein Sequence and Structure, Dayhoff, Ed., NDRF, Washington, Vol. 5, suppl. 3, p. 345, 1978).

On page 10, paragraph [0038]: The invention provides polypeptide fragments of the disclosed proteins. Polypeptide fragments of the invention can comprise at least 8, 10, 12, 15, 18, 19, 20, 25, 50, 75, 100, or 108 contiguous amino acids of an amino acid sequence encoded by a nucleic acid sequence comprising the sequence contained in Figure 1 (~~SEQ ID NO 1~~ SEQ ID NO:1). Also included are intermediate length fragments in this range, such as 51, 52, 53, etc.; 70, 71, 72, etc.; and 100, 101, 102, etc., which are exemplary only and not limiting.

On page 10-11, paragraph [0039]: Variants of the SHINC-1 polypeptide disclosed herein can also occur. Variants can be naturally or non-naturally occurring. Naturally occurring variants are found in humans or other species and comprise amino acid sequences which are substantially identical to the amino acid sequence shown in Figure 1 (~~SEQ ID NO 1~~ SEQ ID NO:1). Species homologs of the protein can be obtained using subgenomic polynucleotides of the invention, as described below, to make suitable probes or primers to screening cDNA expression libraries from other species, such as mice, monkeys, yeast, or bacteria, identifying cDNAs which encode homologs of the protein, and expressing the cDNAs as is known in the art.

On page 11, paragraph [0040]: Non-naturally occurring variants which retain substantially the same biological activities as naturally occurring protein variants are also included here. Preferably, naturally or non-naturally occurring variants have amino acid sequences which are at least 85%, 90%, or 95% identical to the amino acid sequence encoded by a nucleic acid sequence comprising the sequence shown in Figure 1 (~~SEQ ID NO 1~~ SEQ ID NO:1). More preferably, the molecules are at least 96%, 97%, 98% or 99% identical. Percent identity is determined using any method known in the art. A non-limiting example is the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 1. The Smith-

Waterman homology search algorithm is taught in Smith and Waterman, *Adv. Appl. Math.* (1981) 2:482-489.

On page 12, paragraph [0043]: It is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the biological properties of the resulting secreted protein or polypeptide variant. Properties and functions of SHINC-1 or polypeptide variants are of the same type as a protein comprising the amino acid sequence encoded by a nucleic acid sequence comprising the nucleotide sequence shown in Figure 1 (~~SEQ ID NO 1~~ SEQ ID NO:1), although the properties and functions of variants can differ in degree.

On page 14, paragraph [0051]: A fusion protein comprises two protein segments fused together by means of a peptide bond. Amino acid sequences for use in fusion proteins of the invention can utilize the amino acid sequence encoded by a nucleic acid sequence comprising the sequence shown in Figure 1 (~~SEQ ID NO 1~~ SEQ ID NO:1) or can be prepared from biologically active variants such as those described above. The first protein segment can consist of a full-length SHINC-1 or a portion thereof.

On page 14-15, paragraph [0052]: Other first protein segments can consist of at least 8, 10, 12, 15, 18, 19, 20, 25, 50, 75, 100, 108 contiguous amino acids selected from the sequence encoded by the nucleic acid sequence shown in Figure 1 ~~SEQ ID NO 1~~ SEQ ID NO:1. The contiguous amino acids listed herein are not limiting and also include all intermediate lengths such as 20, 21, 22, etc.; 70, 71, 72, etc.

On page 15, paragraph [0054]: These fusions can be made, for example, by covalently linking two protein segments or by standard procedures in the art of molecular biology. Recombinant DNA methods can be used to prepare fusion proteins, for example, by making a DNA construct which comprises a coding sequence comprising the sequence contained in Figure 1 (~~SEQ ID NO 1~~ SEQ ID NO:1) in proper reading frame with a nucleotide encoding the second protein segment and expressing the DNA construct in a host cell, as is known in the art. Many kits for constructing fusion proteins are available from companies that supply research labs with tools for experiments, including, for example, Promega Corporation (Madison, WI), Stratagene (La Jolla, CA), Clontech (Mountain View, CA), Santa Cruz Biotechnology (Santa Cruz, CA), MBL International Corporation (MIC; Watertown, MA), and Quantum Biotechnologies (Montreal, Canada; 1-888-DNA-KITS).

On page 15-16, paragraph [0055]: Proteins, fusion proteins, or polypeptides of the invention can be produced by recombinant DNA methods. For production of recombinant proteins, fusion proteins, or polypeptides, a coding sequence of the nucleotide sequence ~~shown in Figure 1 (SEQ ID NO 1)~~ SEQ ID NO:1 can be expressed in prokaryotic or eukaryotic host cells using expression systems known in the art. These expression systems include bacterial, yeast, insect, and mammalian cells.

On page 17, paragraph [0062]: The invention also provides polynucleotide probes which can be used to detect complementary nucleotides sequences, for example, in hybridization protocols such as Northern or Southern blotting or *in situ* hybridizations. Polynucleotide probes of the invention comprise at least 12, 13, 14, 15, 16, 17, 18, 19, 20, 30, or 40 or more contiguous nucleotides of the sequence contained in Figure 1 (~~SEQ ID NO 1~~ SEQ ID NO:1). Polynucleotide probes of the invention can comprise a detectable label, such as a radioisotopic, fluorescent, enzymatic, or chemiluminescent label.

On page 17, paragraph [0063]: Isolated genes corresponding to the cDNA sequences disclosed herein are also provided. Standard molecular biology methods can be used to isolate the corresponding genes using the cDNA sequences provided herein. These methods include preparation of probes or primers from the nucleotide sequence shown in Figure 1 (~~SEQ ID NO 1~~ SEQ ID NO:1) for use in identifying or amplifying the genes from mammalian, including human, genomic libraries or other sources of human genomic DNA.

On page 20, paragraph [0072]: The targeting sequence is a segment of at least 10, 12, 15, 20, or 50 contiguous nucleotides from the nucleotide sequence shown in Figure 1 (~~SEQ ID NO 1~~ SEQ ID NO:1). The transcription unit is located upstream to a coding sequence of the endogenous gene. The exogenous regulatory sequence directs transcription of the coding sequence of the endogenous gene.